Summary Product Characteristics (SPC)

1. NAME OF THE MEDICINAL PRODUCT

Atorva AM 5/10

Amlodipine Besylate and Atorvastatin Calcium Tablets 5mg/10mg

Atorva AM 5/20

Amlodipine Besylate and Atorvastatin Calcium Tablets 5mg/20mg

Atorva AM 10/20

Amlodipine Besylate and Atorvastatin Calcium Tablets 10mg/20mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Atorva AM 5/10

Amlodipine Besylate and Atorvastatin Calcium Tablets 5mg/10mg

Each film coated tablet contains:

Amlodipine Besylate USP equivalent to Amlodipine and Atorvastatin

Atorva AM 5/20

Amlodipine Besylate and Atorvastatin Calcium Tablets 5mg/20mg

Each film coated tablet contains:

Amlodipine Besylate USP equivalent to Amlodipine and Atorvastatin

Atorva AM 10/20

Amlodipine Besylate and Atorvastatin Calcium Tablets 10mg/20mg

Each film coated tablet contains:

Amlodipine Besylate USP equivalent to Amlodipine and Atovastatin

For full list excipients, see section 6.1

3. PHARMACEUTICAL FORM

Film coated Tablets

Amlodipine Besylate and Atorvastatin Calcium Tablets 5mg/10mg

White to off- white, oval shaped, biconvex film coated tablet plain on both sides. The tablet should be free of all physical defects.

Amlodipine Besylate and Atorvastatin Calcium Tablets 5mg/20mg

White to off- white, oval shaped, biconvex film coated tablet plain on both sides. The tablet should be free of all physical defects.

Amlodipine Besylate and Atorvastatin Calcium Tablets 10mg/20mg

Light blue to blue colored, oval shaped, biconvex film coated tablet plain on both sides. The tablet should be free of all physical defects.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Amlodipine Besylate and Atorvastatin Calcium Tablets is a combination of amlodipine besylate, a calcium channel blocker, and atorvastatin calcium, a HMG CoA-reductase inhibitor, indicated in patients for whom treatment with both amlodipine and atorvastatin is appropriate.

Amlodipine is indicated for the treatment of hypertension, to lower blood pressure. Lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions. Amlodipine is indicated for the treatment of coronary artery disease.

Atorvastatin is indicated as an adjunct therapy to diet for prevention of cardiovascular disease and hyperlipidemia.

4.2 Posology and method of administration

Dosage of Amlodipine Besylate and Atorvastatin Calcium Tablets must be individualized on the basis of both effectiveness and tolerance for each individual component in the treatment of hypertension/angina and hyperlipidemia. Select doses of amlodipine and atorvastatin independently.

Amlodipine Besylate and Atorvastatin Calcium Tablets may be substituted for its individually titrated components. Patients may be given the equivalent dose of Amlodipine Besylate and Atorvastatin Calcium Tablets or a dose of Amlodipine Besylate and Atorvastatin Calcium Tablets with increased amounts of amlodipine, atorvastatin, or both for additional antianginal effects, blood pressure lowering, or lipid-lowering effect.

Amlodipine Besylate and Atorvastatin Calcium Tablets may be used to provide additional therapy for patients already on one of its components. Amlodipine Besylate and Atorvastatin Calcium Tablets may be used to initiate treatment in patients with hyperlipidemia and either hypertension or angina.

Amlodipine The usual initial antihypertensive oral dose of amlodipine is 5 mg once daily, and the maximum dose is 10 mg once daily.

Pediatric (age > 6 years), small adult, fragile, or elderly patients, or patients with hepatic insufficiency may be started on 2.5 mg once daily and this dose may be used when adding amlodipine to other antihypertensive therapy.

Adjust dosage according to blood pressure goals. In general, wait 7 to 14 days between titration steps. Titration may proceed more rapidly, however, if clinically warranted, provided the patient is assessed frequently.

Angina: The recommended dose of amlodipine for chronic stable or vasospastic angina is 5–10 mg, with the lower dose suggested in the elderly and in patients with hepatic insufficiency. Most patients will require 10 mg for adequate effect.

Coronary Artery Disease: The recommended dose range of amlodipine for patients with CAD is 5–10 mg once daily. In clinical studies, the majority of patients required 10mg.

Pediatrics: The effective antihypertensive oral dose of amlodipine in pediatric patients ages 6–17 years is 2.5mg to 5mg once daily. Doses in excess of 5 mg daily have not been studied in pediatric patients.

Atorvastatin (Hyperlipidemia) Hyperlipidemia (Heterozygous Familial and Nonfamilial) and Mixed Dyslipidemia (Fredrickson Types IIa and IIb): The recommended starting dose of atorvastatin is 10 or 20 mg once daily. Patients who require a large reduction in LDL-C (more than 45%) may be started at 40 mg once daily. The dosage range of atorvastatin is 10 to 80 mg once daily. Atorvastatin can be administered as a single dose at any time of the day, with or without food. The starting dose and maintenance doses of atorvastatin should be individualized according to patient characteristics such as goal of therapy and response. After initiation and/or upon titration of atorvastatin, lipid levels should be analyzed within 2 to 4 weeks and dosage adjusted accordingly.

Homozygous Familial Hypercholesterolemia: The dosage range of atorvastatin in patients with homozygous FH is 10 to 80 mg daily. Atorvastatin should be used as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) in these patients or if such treatments are unavailable.

Concomitant Lipid-Lowering Therapy: Atorvastatin may be used with bile acid resins. Monitor for signs of myopathy in patients receiving the combination of HMG-CoA reductase inhibitors (statins) and fibrates.

Patients with Renal Impairment: Renal disease does not affect the plasma concentrations nor LDL-C reduction of atorvastatin; thus, dosage adjustment in patients with renal dysfunction is not necessary.

Use with Cyclosporine, Clarithromycin, Itraconazole, or Certain Protease Inhibitors: In patients taking cyclosporine or the HIV protease inhibitors (tipranavir plus ritonavir) or the hepatitis C protease inhibitor (telaprevir), avoid therapy with atorvastatin. In patients with HIV taking lopinavir plus ritonavir, use the lowest necessary dose of atorvastatin. In patients taking clarithromycin, itraconazole, or in patients with HIV taking a combination of saquinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, or fosamprenavir plus ritonavir, limit therapy with atorvastatin to 20 mg, and make appropriate clinical assessment to ensure that the lowest dose necessary of atorvastatin is employed. In patients taking the HIV protease inhibitor nelfinavir or the hepatitis C

protease inhibitor boceprevir, limit therapy with atorvastatin to 40 mg, and make appropriate clinical assessment to ensure that the lowest dose necessary of atorvastatin is employed.

Heterozygous Familial Hypercholesterolemia in Pediatric Patients (10–17 years of age): The recommended starting dose of atorvastatin is 10 mg/day; the maximum recommended dose is 20 mg/day (doses greater than 20 mg have not been studied in this patient population). Doses should be individualized according to the recommended goal of therapy. Adjustments should be made at intervals of 4 weeks or more.

4.3 Contraindications

Active Liver Disease

Atorvastatin is contraindicated in patients with active liver disease, which may include unexplained persistent elevations in hepatic transaminase levels.

Pregnancy

Atorvastatin is contraindicated in women who are pregnant or may become pregnant. Atorvastatin may cause fetal harm when administered to a pregnant woman. Serum cholesterol and triglycerides increase during normal pregnancy, and cholesterol or cholesterol derivatives are essential for fetal development. Atherosclerosis is a chronic process and

discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia.

There are no adequate and well-controlled studies of atorvastatin use during pregnancy; however, in rare reports congenital anomalies were observed following intrauterine exposure to statins. In rat and rabbit animal reproduction studies, atorvastatin revealed no evidence of teratogenicity. Amlodipine Besylate and Atorvastatin Calcium Tablets should be administered to women of child bearing age only when such patients are highly unlikely to conceive and have been informed of the potential hazard. If the patient becomes pregnant while taking this drug, therapy should be discontinued immediately and the patient apprised of the potential hazard to the fetus.

Nursing Mothers

It is not known whether atorvastatin or amlodipine are excreted into human milk; however, a small amount of another statin does pass into breast milk. Because statins have the potential for serious adverse reactions in nursing infants, women taking Amlodipine Besylate and Atorvastatin Calcium Tablets should not breastfeed their infants.

4.4 Special warnings and precautions for use

Myopathy and Rhabdomyolysis

Rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported with atorvastatin and with other drugs in this class. A history of renal impairment may be a risk factor for the development of rhabdomyolysis. Such patients merit closer monitoring for skeletal muscle effects.

Atorvastatin, like other statins, occasionally causes myopathy, defined as muscle aches or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values > 10 times upper limit of normal [ULN]. The concomitant use of higher doses of atorvastatin with certain drugs such as cyclosporine and strong CYP3A4 inhibitors (e.g., clarithromycin, itraconazole, and HIV protease inhibitors) increases the risk of myopathy/rhabdomyolysis.

There have been rare reports of immune-mediated necrotizing myopathy (IMNM), an autoimmune myopathy, associated with statin use. IMNM is characterized by: proximal muscle weakness and elevated serum creatine kinase, which persist despite discontinuation of statin treatment; muscle

biopsy showing necrotizing myopathy without significant inflammation; improvement with immunosuppressive agents.

Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, or marked elevation of CPK. Patients should be advised to report promptly unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever or if muscle signs and symptoms persist after discontinuing amlodipine besylate and atorvastatin calcium tablets. Amlodipine besylate and atorvastatin calcium tablets therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected.

The risk of myopathy during treatment with statins is increased with concurrent administration of cyclosporine, fibric acid derivatives, erythromycin, clarithromycin, the hepatitis C protease inhibitor telaprevir, combinations of HIV protease inhibitors, including saquinavir plus ritonavir, lopinavir plus ritonavir, tipranavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, and fosamprenavir plus ritonavir, niacin, or azole antifungals. Physicians considering combined therapy with amlodipine besylate and atorvastatin calcium tablets and fibric acid derivatives, erythromycin, clarithromycin, a combination of saquinavir plus ritonavir, lopinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, or fosamprenavir plus ritonavir, azole antifungals, or lipid-modifying doses of niacin should carefully weigh the potential benefits and risks and should carefully monitor patients for any signs or symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy and during any periods of upward dosage titration of either drug. Lower starting and maintenance doses of atorvastatin should be considered

when taken concomitantly with the aforementioned drugs. Periodic creatine phosphokinase (CPK) determinations may be considered in such situations, but there is no assurance that such monitoring will prevent the occurrence of severe myopathy.

Prescribing recommendations for interacting agents are summarized in below Table.

Cyclosporine, HIV protease inhibitors (tipranavir plus ritonavir), hepatitis C protease inhibitor (telaprevir)	Avoid atorvastatin
HIV protease inhibitor (lopinavir plus ritonavir)	Use with caution and lowest dose necessary
Clarithromycin, itraconazole, HIV protease inhibitors (saquinavir plus ritonavir*, darunavir plus	Do not exceed 20 mg atorvastatin daily

ritonavir, fosamprenavir, fosamprenavir plus ritonavir)	
HIV protease inhibitor (nelfinavir) Hepatitis C protease inhibitor (boceprevir)	Do not exceed 40 mg atorvastatin daily

* Use with caution and with the lowest dose necessary

Cases of myopathy, including rhabdomyolysis, have been reported with atorvastatin co-administered with colchicine, and caution should be exercised when prescribing atorvastatin with colchicine.

Withhold or discontinue in any patient with an acute, serious condition suggestive of a myopathy or having a risk factor predisposing to the development of renal failure secondary to rhabdomyolysis (e.g., severe acute infection; hypotension; major surgery; trauma; severe metabolic, endocrine, and electrolyte disorders; and uncontrolled seizures).

Liver Dysfunction

Statins, like atorvastatin, and some other lipid-lowering therapies, have been associated with biochemical abnormalities of liver function. Persistent elevations (>3 times the upper limit of normal [ULN] occurring on 2 or more occasions) in serum transaminases occurred in 0.7% of patients who received atorvastatin in clinical trials. The incidence of these abnormalities was 0.2%, 0.2%, 0.6%, and 2.3% for 10, 20, 40, and 80 mg, respectively.

One patient in clinical trials with atorvastatin developed jaundice. Increases in liver function tests (LFT) in other patients were not associated with jaundice or other clinical signs or symptoms. Upon dose reduction, drug interruption, or discontinuation, transaminase levels returned to or near pretreatment levels without sequelae. Eighteen of 30 patients with persistent LFT elevations continued treatment with a reduced dose of atorvastatin.

It is recommended that liver enzyme tests be obtained prior to initiating therapy with atorvastatin and repeated as clinically indicated. There have been rare post marketing reports of fatal and non-fatal hepatic failure in patients taking statins, including atorvastatin. If serious liver injury with clinical symptoms and/or hyperbilirubinemia or jaundice occurs during treatment with amlodipine besylate and atorvastatin calcium tablets,

promptly interrupt therapy. If an alternate etiology is not found, do not restart amlodipine besylate and atorvastatin calcium tablets.

Active liver disease or unexplained persistent transaminase elevations are contraindications to the use of amlodipine besylate and atorvastatin calcium tablets.

Increased Angina and Myocardial Infarction

Worsening angina and acute myocardial infarction can develop after starting or increasing the dose of amlodipine, particularly in patients with severe obstructive coronary artery disease.

Hypotension

Symptomatic hypotension is possible with use of amlodipine, particularly in patients with severe aortic stenosis. Because of the gradual onset of action, acute hypotension is unlikely.

Endocrine Function

Increases in HbA1c and fasting serum glucose levels have been reported with HMG-CoA reductase inhibitors, including atorvastatin.

Statins interfere with cholesterol synthesis and theoretically might blunt adrenal and/or gonadal steroid production. Clinical studies have shown that atorvastatin does not reduce basal plasma cortisol concentration or impair adrenal reserve. The effects of statins on male fertility have not been studied in adequate numbers of patients. The effects, if any, on the pituitary-gonadal axis in premenopausal women are unknown. Avoid a statin with drugs that may decrease the levels or activity of endogenous steroid hormones such as ketoconazole, spironolactone, and cimetidine.

CNS Toxicity

Brain hemorrhage was seen in a female dog treated with atorvastatin for 3 months at 120 mg/kg/day. Brain hemorrhage and optic nerve vacuolation were seen in another female dog that was sacrificed in moribund condition after 11 weeks of escalating doses up to 280mg/kg/day. The 120 mg/kg dose resulted in a systemic exposure approximately 16 times the human plasma area-under-the-curve (AUC, 0–24 hours) based on the maximum human dose of 80mg/day. A single tonic convulsion was seen in each of 2 male dogs (one treated at 10 mg/kg/day and one at 120mg/kg/day) in a 2-year study. No CNS lesions have been observed in mice after chronic treatment for up to 2 years at doses up to 400mg/kg/day or in rats at doses up to 100mg/kg/day. These doses were 6 to 11 times (mouse) and 8 to 16 times (rat) the

human AUC (0–24) based on the maximum recommended human dose of 80mg/day.

CNS vascular lesions, characterized by perivascular hemorrhages, edema, and mononuclear cell infiltration of perivascular spaces, have been observed in dogs treated with other statins. A chemically similar drug in this class produced optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in clinically normal dogs in a dose-dependent fashion at a dose that produced plasma drug levels about 30 times higher than the mean drug level in humans taking the highest recommended dose.

Hemorrhagic Stroke

In a post-hoc analysis of the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) study where atorvastatin 80mg vs. placebo was administered in 4,731 subjects without CHD who had a stroke or TIA within the preceding 6 months, a higher incidence of hemorrhagic stroke was seen in the atorvastatin 80mg group compared to placebo (55, 2.3% atorvastatin vs. 33, 1.4% placebo; HR: 1.68, 95% CI: 1.09, 2.59; p=0.0168). The incidence of fatal hemorrhagic stroke was similar across treatment groups (17 vs. 18 for the atorvastatin and placebo groups, respectively). The incidence of non-fatal hemorrhagic stroke was significantly higher in the atorvastatin group (38, 1.6%) as compared to the placebo group (16, 0.7%). Some baseline characteristics, including hemorrhagic and lacunar stroke on study entry, were associated with a higher incidence of hemorrhagic stroke in the atorvastatin group.

4.5 Interaction with other medicinal products and other forms of interaction

Data from a drug-drug interaction study involving 10 mg of amlodipine and 80 mg of atorvastatin in healthy subjects indicate that the pharmacokinetics of amlodipine are not altered when the drugs are co-administered. The effect of amlodipine on the pharmacokinetics of atorvastatin showed no effect on the Cmax: 91% (90% confidence interval: 80 to 103%), but the AUC of atorvastatin increased by 18% (90% confidence interval: 109 to 127%) in the presence of amlodipine, which is not clinically meaningful.

No drug interaction studies have been conducted with amlodipine besylate and atorvastatin calcium tablets and other drugs, although studies have been conducted in the individual amlodipine and atorvastatin components, as described below:

Amlodipine

Impact of Other Drugs on Amlodipine

CYP3A Inhibitors

Co-administration with CYP3A inhibitors (moderate and strong) results in increased systemic exposure to amlodipine and may require dose reduction. Monitor for symptoms of hypotension and edema when amlodipine is co-administered with CYP3A inhibitors to determine the need for dose adjustment.

CYP3A Inducers

No information is available on the quantitative effects of CYP3A inducers on amlodipine. Blood pressure should be closely monitored when amlodipine is co-administered with CYP3A inducers.

Sildenafil

Monitor for hypotension when sildenafil is co-administered with amlodipine.

Impact of Amlodipine on Other Drugs

Immunosuppressants

Amlodipine may increase the systemic exposure of cyclosporine or tacrolimus when co-administered. Frequent monitoring of trough blood levels of cyclosporine and tacrolimus is recommended and adjust the dose when appropriate.

Atorvastatin

The risk of myopathy during treatment with statins is increased with concurrent administration of fibric acid derivatives, lipid-modifying doses of niacin, cyclosporine, or strong CYP3A4 inhibitors (e.g., clarithromycin, HIV protease inhibitors, and itraconazole).

Strong Inhibitors of CYP3A4

Atorvastatin is metabolized by CYP3A4. Concomitant administration of atorvastatin with strong inhibitors of CYP3A4 can lead to increases in plasma concentrations of atorvastatin. The extent of interaction and potentiation of effects depend on the variability of effect on CYP3A4.

Clarithromycin: Atorvastatin AUC was significantly increased with concomitant administration of atorvastatin 80 mg with clarithromycin

(500 mg twice daily) compared to that of atorvastatin alone. Therefore, in patients taking clarithromycin, avoid atorvastatin doses >20 mg.

Combination of Protease Inhibitors: Atorvastatin AUC was significantly increased with concomitant administration of atorvastatin with several combinations of HIV protease inhibitors, as well as with the hepatitis C protease inhibitor telaprevir, compared to that of atorvastatin alone. Therefore, in patients taking the HIV protease inhibitor tipranavir plus ritonavir, or the hepatitis C protease inhibitor telaprevir, concomitant use of atorvastatin should be avoided. In patients taking the HIV protease inhibitor lopinavir plus ritonavir, caution should be used when prescribing atorvastatin and the lowest dose necessary should be used. In patients taking the HIV protease inhibitors saquinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, or fosamprenavir plus ritonavir, the dose of atorvastatin should not exceed 20 mg. In patients taking the HIV protease inhibitor nelfinavir or the hepatitis C protease inhibitor boceprevir, the dose of atorvastatin should not exceed 40 mg and close clinical monitoring is recommended.

Itraconazole: Atorvastatin AUC was significantly increased with concomitant administration of atorvastatin 40 mg and itraconazole 200 mg. Therefore, in patients taking itraconazole, avoid atorvastatin doses > 20 mg.

Grapefruit Juice

Contains one or more components that inhibit CYP3A4 and can increase plasma concentrations of atorvastatin, especially with excessive grapefruit juice consumption (> 1.2 liters per day).

Cyclosporine

Atorvastatin and atorvastatin-metabolites are substrates of the OATP1B1 transporter. Inhibitors of the OATP1B1 (e.g., cyclosporine) can increase the bioavailability of atorvastatin. Atorvastatin AUC was significantly increased with concomitant administration of atorvastatin 10 mg and cyclosporine 5.2 mg/kg/day compared to that of atorvastatin alone. The co-administration of atorvastatin with cyclosporine should be avoided.

Gemfibrozil

Because of an increased risk of myopathy/rhabdomyolysis when HMG-CoA reductase inhibitors are co-administered with gemfibrozil, avoid concomitant administration of atorvastatin with gemfibrozil.

Other Fibrates

The risk of myopathy during treatment with HMG-CoA reductase inhibitors is increased with concurrent administration of other fibrates.

Niacin

The risk of skeletal muscle effects may be enhanced when atorvastatin is used in combination with niacin; consider a reduction in atorvastatin dosage in this setting.

Rifampin or other Inducers of CYP3A4

Concomitant administration of atorvastatin with inducers of CYP3A4 (e.g., efavirenz, rifampin) can lead to variable reductions in plasma concentrations of atorvastatin. Because of the dual interaction mechanism of rifampin, simultaneous co-administration of atorvastatin with rifampin is recommended, as delayed administration of atorvastatin after administration of rifampin has been associated with a significant reduction in atorvastatin plasma concentrations.

Digoxin

When multiple doses of atorvastatin and digoxin were co-administered, steady-state plasma digoxin concentrations increased by approximately 20%. Monitor digoxin levels.

Oral Contraceptives

Co-administration of atorvastatin and an oral contraceptive increased AUC values for norethindrone and ethinyl estradiol. Consider these increases when selecting an oral contraceptive for a woman taking amlodipine besylate and atorvastatin calcium tablets.

Warfarin

Atorvastatin had no clinically significant effect on prothrombin time when administered to patients receiving chronic warfarin treatment.

Colchicine

Cases of myopathy, including rhabdomyolysis, have been reported with atorvastatin co-administered with colchicine.

4.6 Pregnancy and lactation

Pregnancy

Atorvastatin is contraindicated in women who are pregnant or may become pregnant. Atorvastatin may cause fetal harm when administered to a pregnant woman. Amlodipine besylate and atorvastatin calcium

tablets should be administered to women of child bearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards. If the woman becomes pregnant while taking amlodipine besylate and atorvastatin calcium tablets, it should be discontinued immediately and the patient advised again as to the potential hazards to the fetus, and the lack of known clinical benefit with continued use during pregnancy.

Serum cholesterol and triglycerides increase during normal pregnancy, and cholesterol products are essential for fetal development. Atherosclerosis is a chronic process, and discontinuation of lipid-lowering drugs during pregnancy should have little impact on long-term outcomes of primary hypercholesterolemia therapy.

Amlodipine

There are no adequate and well-controlled studies in pregnant women. Amlodipine should be used during pregnancy only if the potential benefit justifies the risk to the fetus.

No evidence of teratogenicity or other embryo/fetal toxicity was found when pregnant rats and rabbits were treated orally with amlodipine maleate at doses up to 10 mg amlodipine/kg/day (respectively, 8 times * and 23 times* the maximum recommended human dose of 10 mg on a mg/m2 basis) during their respective periods of major organogenesis. However, litter size was significantly decreased (by about 50%) and the number of intrauterine deaths was significantly increased (about 5-fold) in rats receiving amlodipine maleate at a dose equivalent to 10 mg amlodipine/kg/day for 14 days before mating and throughout mating and gestation. Amlodipine maleate has been shown to prolong both the gestation period and the duration of labor in rats at this dose.

*Based on patient weight of 50 kg.

Atorvastatin

There are no adequate and well-controlled studies of atorvastatin use during pregnancy. There have been rare reports of congenital anomalies following intrauterine exposure to statins. In a review of about 100 prospectively followed pregnancies in women exposed to other statins, the incidences of congenital anomalies, spontaneous abortions, and fetal deaths/stillbirths did not exceed the rate expected in the general population. However, this study was only able to exclude a three to four-fold increased risk of congenital anomalies over background incidence. In 89% of these cases, drug treatment started before pregnancy and stopped during the first trimester when pregnancy was identified.

Atorvastatin crosses the rat placenta and reaches a level in fetal liver equivalent to that of maternal plasma. Atorvastatin was not teratogenic in rats at doses up to 300 mg/kg/day or in rabbits at doses up to 100 mg/kg/day. These doses resulted in multiples of about 30 times (rat) or 20 times (rabbit) the human exposure based on surface area (mg/m2)

In a study in rats given atorvastatin calcium at doses equivalent to 20, 100, or 225 mg/kg/day, from gestation day 7 through to lactation day 21 (weaning), there was decreased pup survival at birth, neonate, weaning, and maturity in pups of mothers dosed with 225 mg/kg/day. Body weight was decreased on days 4 and 21 in pups of mothers dosed at 100 mg/kg/day; pup body weight was decreased at birth and at days 4, 21, and 91 at 225 mg/kg/day. Pup development was delayed (rotorod performance at 100 mg/kg/day and acoustic startle at 225 mg/kg/day; pinnae detachment and eye-opening at 225 mg/kg/day). These doses of atorvastatin correspond to 6 times (100 mg/kg) and 22 times (225 mg/kg) the human AUC at 80 mg/day.

No studies have been conducted in pregnant women on the effect of amlodipine besylate and atorvastatin calcium tablets, amlodipine, or atorvastatin on the mother or the fetus during labor or delivery, or on the duration of labor or delivery. Amlodipine has been shown to prolong the duration of labor in rats.

Lactation

It is not known whether amlodipine is excreted in human milk. In the absence of this information, it is recommended that nursing be discontinued while amlodipine besylate and atorvastatin calcium tablets are administered.

It is not known whether atorvastatin is excreted in human milk, but a small amount of another drug in this class does pass into breast milk. Nursing rat pups had plasma and liver drug levels of 50% and 40%, respectively, of that in their mother's milk. Animal breast milk drug levels may not accurately reflect human breast milk levels. Because another drug in this class passes into human milk and because statins have a potential to cause serious adverse reactions in nursing infants, women taking amlodipine besylate and atorvastatin calcium tablets should be advised not to nurse their infants.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

Amlodipine besylate and atorvastatin calcium tablets have been evaluated for safety in 1,092 patients in double-blind placebo-controlled studies treated for co-morbid hypertension and dyslipidemia. In general, treatment with amlodipine besylate and atorvastatin calcium tablets was well tolerated. For the most part, adverse reactions have been mild or moderate in severity. In clinical trials with amlodipine besylate and atorvastatin calcium tablets, no adverse reactions peculiar to this combination have been observed. Adverse reactions are similar in terms of nature, severity, and frequency to those reported previously with amlodipine and atorvastatin.

General:

The most common side effect of amlodipine is edema.

The most common side effects of atorvastatin are diarrhea, nasopharyngitis, and arthralgia.

Gastrointestinal

Common (1% to 10%): Abdominal pain, constipation, diarrhea, dyspepsia, nausea Uncommon (0.1% to 1%): Flatulence

Amlodipine:

Common (1% to 10%): Nausea, abdominal pain, constipation, dyspepsia

Uncommon (0.1% to 1%): Dysphagia, diarrhea, flatulence, pancreatitis, vomiting, gingival hyperplasia, dry mouth, flatulence, altered bowel habits

Frequency not reported: Gastritis, loose stools

Atorvastatin:

Very common (10% or more): Diarrhea (up to 14.1%)

Common(1% to10%):Dyspepsia,nausea, abdominal pain, constipation, flatulence

Uncommon (0.1% to 1%): Abdominal discomfort, vomiting

Rare (less than 0.1%): Eructation Respiratory

Common (1% to 10%): Respiratory tract infection Uncommon (0.1% to 1%): Pharyngitis, rhinitis

Amlodipine:

Common (1% to 10%): Epistaxis, respiratory tract infection

Uncommon (0.1% to 1%): Dyspnea, pharyngitis, rhinitis

Frequency not reported: Coughing

Atorvastatin:

Very common (10% or more): Nasopharyngitis (up to 12.9%)

Common (1% to 10%): Pharyngolaryngeal pain, respiratory tract infection, rhinitis Uncommon (0.1% to 1%): Pharyngitis, asthma

Rare (less than 0.1%): Sinusitis

Frequency not reported: Epistaxis, interstitial lung disease Musculoskeletal

Common (1% to 10%): Back pain, arthralgia, myalgia Uncommon (0.1% to 1%): Leg cramps

Amlodipine:

Common (1% to 10%): Back pain, myalgia, arthralgia

Uncommon (0.1% to 1%): Arthrosis, muscle cramps, leg cramps

Frequency not reported: Muscle weakness, twitching

Atorvastatin:

Very common (10% or more): Arthralgia (up to 11.7%)

Common (1% to 10%): Pain in extremity, musculoskeletal pain, muscle spasms, myalgia, back pain

Uncommon (0.1% to 1%): Creatine kinase elevations 10 times the upper limit of normal or greater, leg cramps, neck pain Rare (less than 0.1%): Myositis, myopathy, muscle fatigue

Frequency not reported: Joint swelling, blood creatinephosphokinase increased

Post marketing reports: Rhabdomyolysis, tendon rupture, immune-mediated necrotizing myopathy

Other Common (1% to 10%): Accidental injury, asthenia, pain Uncommon (0.1% to 1%): Vertigo

Amlodipine:

Very common (10% or more): Edema (up to 10.8%)

Common (1% to 10%): Fatigue, accidental injury, asthenia, pain

Uncommon (0.1% to 1%): Vertigo, malaise, rigors, tinnitus, gynecomastia

Atorvastatin:

Common (1% to 10%): Accidental injury, asthenia

Uncommon (0.1% to 1%): Pain, vertigo, deafness, malaise

Rare (less than 0.1%): Tinnitus, pyrexia

Post marketing reports: Fatigue, gynecomastia Cardiovascular

Common (1% to 10%): Palpitation, vasodilation, peripheral edema

Uncommon (0.1% to 1%): Hypertension

Amlodipine:

Common (1% to 10%): Flushing, palpitation, peripheral edema

Uncommon (0.1% to 1%): Arrhythmia, bradycardia, chest pain, peripheral ischemia, tachycardia, vasculitis, hot flushes, vasodilation, hypotension, postural hypotension

Frequency not reported: Cardiac failure, pulse irregularity, extrasystoles, myocardial infarction

Atorvastatin:

Common (1% to 10%): Hypertension, palpitation

Uncommon (0.1% to 1%): Vasodilation

Post marketing reports: Chest pain, peripheral edema Hepatic

Common (1% to 10%): GGT increased, ALT increased, AST increased Amlodipine:

Uncommon (0.1% to 1%): GGT increased, ALT increased, AST increased, pancreatitis Post marketing reports: Jaundice, hepatic enzyme elevations, hepatitis

Atorvastatin:

Common (1% to 10%): Transaminase elevations 3 times the upper limit of normal or greater twice within 4 to 10 days

Uncommon (0.1% to 1%): GGT increased, ALT increased, AST increased

Rare (less than 0.1%): Pancreatitis, hepatitis, cholestasis

Frequency not reported: Transaminases increased, liver function test abnormal, blood alkaline phosphatase increased

Post marketing reports: Fatal and non-fatal hepatic failure

Nervous system

Common (1% to 10%): Headache, dizziness

Uncommon (0.1% to 1%): Paresthesia

Amlodipine:

Common (1% to 10%): Dizziness, somnolence, headache

Uncommon (0.1% to 1%): Syncope, hypoesthesia, neuropathy peripheral, paresthesia, tremor, postural dizziness

Frequency not reported: Ataxia, hypertonia, migraine, amnesia, parosmia, taste perversion

Post marketing reports: Extrapyramidal disorder Atorvastatin:

Common (1% to 10%): Hemorrhagic stroke, headache, dizziness

Uncommon (0.1% to 1%): Hypoesthesia, paresthesia

Rare (less than 0.1%): Peripheral neuropathy

Post marketing reports: Cognitive impairment, amnesia, dysgeusia Immunologic

Common (1% to 10%): Flu syndrome

Uncommon (0.1% to 1%): Allergic reaction

Amlodipine:

Common (1% to 10%): Allergic reaction

Uncommon (0.1% to 1%): Flu syndrome

Atorvastatin:

Common (1% to 10%): Flu syndrome

Uncommon (0.1% to 1%): Allergic reaction, infection, influenza Rare (less than 0.1%): Hypersensitivity, anaphylaxis Dermatologic

Common (1% to 10%): Rash

Amlodipine:

Common (1% to 10%): Rash, rash erythematous

Uncommon (0.1% to 1%): Angioedema, erythema multiforme, pruritus, rash maculopapular, sweating increased, purpura, alopecia

Frequency not reported: Skin discoloration, urticaria, skin dryness, dermatitis, cold and clammy skin

Atorvastatin:

Uncommon (0.1% to 1%): Rash, pruritus, urticarial Rare (less than 0.1%): Angioedema, alopecia

Post marketing reports: Angioneurotic edema, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis Psychiatric

Uncommon (0.1% to 1%): Depression, insomnia

Amlodipine:

Uncommon (0.1% to 1%): Insomnia, nervousness, depression, abnormal dreams, anxiety, depersonalization, mood changes Frequency not reported: Apathy, agitation

Atorvastatin:

Common (1% to 10%): Insomnia

Uncommon (0.1% to 1%): Depression, nightmare Genitourinary

Uncommon (0.1% to 1%): Urinary frequency

Amlodipine:

Common (1% to 10%): Male sexual dysfunction, urinary frequency

Uncommon (0.1% to 1%): Female sexual dysfunction, micturition frequency, micturition disorder, nocturia

Frequency not reported: Dysuria, polyuria

Atorvastatin:

Common (1% to 10%): Urinary tract infection

Uncommon (0.1% to 1%): Urinary frequency, erectile dysfunction Rare (less than 0.1%): White blood cells urine positive

Metabolic

Amlodipine:

Uncommon (0.1% to 1%): Anorexia, weight gain, weight decrease, hyperglycemia, thirst Frequency not reported: Increased appetite

Atorvastatin:

Common (1% to 10%): Diabetes

Uncommon (0.1% to 1%): Anorexia Rare (less than 0.1%): Hypoglycemia Frequency not reported: Hyperglycemia

Post marketing reports: Weight increased Ocular

Amlodipine:

Uncommon (0.1% to 1%): Abnormal vision, conjunctivitis, diplopia, eye pain

Frequency not reported: Abnormal visual accommodation, xerophthalmia

Atorvastatin:

Uncommon (0.1% to 1%): Vision blurred Hematologic

Amlodipine:

Uncommon (0.1% to 1%): Leukopenia, thrombocytopenia

Atorvastatin:

Post marketing reports: Thrombocytopenia

Reporting of suspected adverse reactions: Healthcare professionals are requested to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org.

4.9 Overdose

There is no information on overdosage with amlodipine besylate and atorvastatin calcium tablets in humans.

Amlodipine

Overdosage might be expected to cause excessive peripheral vasodilation with marked hypotension and possibly a reflex

tachycardia. In humans, experience with intentional overdosage of amlodipine is limited.

Single oral doses of amlodipine maleate equivalent to 40 mg amlodipine/kg and 100 mg amlodipine/kg in mice and rats, respectively, caused deaths. Single oral amlodipine maleate doses equivalent to 4 or more mg amlodipine/kg or higher in dogs (11 or more times the

maximum recommended human dose on a mg/m2 basis) caused a marked peripheral vasodilation and hypotension.

If overdose should occur with amlodipine, initiate active cardiac and respiratory monitoring. Perform frequent blood pressure measurements. Should hypotension occur, provide cardiovascular support including elevation of the extremities and administration of fluids. If hypotension remains unresponsive to these conservative measures, consider administration of vasopressors (such as phenylephrine) with specific attention to circulating volume and urine output. As amlodipine is highly protein bound, hemodialysis is not likely to be of benefit.

Atorvastatin

There is no specific treatment for atorvastatin overdosage. In the event of an overdose, the patient should be treated symptomatically, and supportive measures instituted as required. Because of extensive drug binding to plasma proteins, hemodialysis is not expected to significantly enhance atorvastatin clearance.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Calcium Channel Blocker, HMG CoA reductase Inhibitor

ATC code: C10BX03

Mechanism of Action

Amlodipine

Amlodipine binds to both dihydropyridine and nondihydropyridine binding sites. The contractile processes of cardiac muscle and vascular smooth muscle are dependent upon the movement of extracellular calcium ions into these cells through specific ion channels. Amlodipine inhibits calcium ion influx across cell membranes selectively, with a greater effect on vascular smooth muscle cells than on cardiac muscle cells. Negative inotropic effects can be detected in vitro but such effects have not been seen in intact animals at therapeutic doses. Serum calcium concentration is not affected by amlodipine.

Amlodipine is a peripheral arterial vasodilator that acts directly on vascular smooth muscle to cause a reduction in peripheral vascular resistance and reduction in blood pressure.

The precise mechanisms by which amlodipine relieves angina have not been fully delineated, but are thought to include the following:

Exertional Angina: In patients with exertional angina, amlodipine reduces the total peripheral resistance (afterload) against which the heart works and reduces the rate pressure product, and thus myocardial oxygen demand, at any given level of exercise.

Vasospastic Angina: Amlodipine has been demonstrated to block constriction and restore blood flow in coronary arteries and arterioles in response to calcium, potassium epinephrine, serotonin, and thromboxane A2 analog in experimental animal models and in human coronary vessels in vitro. This inhibition of coronary spasm is responsible for the effectiveness of amlodipine in vasospastic (Prinzmetal's or variant) angina.

Atorvastatin

Cholesterol and triglycerides circulate in the bloodstream as part of lipoprotein complexes. With ultracentrifugation, these complexes separate into HDL (high-density lipoprotein), IDL (intermediate-density lipoprotein), LDL (low-density lipoprotein), and VLDL (very-low-density lipoprotein) fractions. Triglycerides (TG) and cholesterol in the liver are incorporated into VLDL and released into the plasma for delivery to peripheral tissues. LDL is formed from VLDL and is catabolized primarily through the high-affinity LDL receptor.

Clinical and pathologic studies show that elevated plasma levels of total cholesterol (total-C), LDL-cholesterol (LDL-C), and apolipoprotein B (apo B) promote human atherosclerosis and are risk factors for developing cardiovascular disease, while increased levels of HDL-C are associated with a decreased cardiovascular risk.

Epidemiologic investigations have established that cardiovascular morbidity and mortality vary directly with the level of total-C and LDL-C, and inversely with the level of HDL-C.

In animal models, atorvastatin lowers plasma cholesterol and lipoprotein levels by inhibiting HMG-CoA reductase and cholesterol synthesis in the liver and by increasing the number of hepatic LDL receptors on the cell surface to enhance uptake and catabolism of LDL; atorvastatin also reduces LDL production and the number of LDL particles.

Atorvastatin reduces total-C, LDL-C, and apo B in patients with homozygous and heterozygous familial hypercholesterolemia (FH), nonfamilial forms of hypercholesterolemia, and mixed dyslipidemia.

Atorvastatin also reduces VLDL-C and TG and produces variable increases in HDL-C and apolipoprotein A-1. Atorvastatin reduces total-C, LDL-C, VLDL-C, apo B, TG, and non-HDL-C, and increases HDL-C in patients with isolated hypertriglyceridemia. Atorvastatin reduces intermediate density lipoprotein cholesterol (IDL-C) in patients with dysbetalipoproteinemia.

Like LDL, cholesterol-enriched triglyceride-rich lipoproteins, including VLDL, (IDL), and remnants, can also promote atherosclerosis. Elevated plasma triglycerides are frequently found in a triad with low HDL-C levels and small LDL particles, as well as in association with non-lipid metabolic risk factors for coronary heart disease. As such, total plasma TG has not consistently been shown to be an independent risk factor for CHD. Furthermore, the independent effect of raising HDL or lowering TG on the risk of coronary and cardiovascular morbidity and mortality has not been determined.

5.2 Pharmacokinetic properties

Absorption

Amlodipine: After oral administration of therapeutic doses of amlodipine alone, absorption produces peak plasma concentrations between 6 and 12 hours. Absolute bioavailability has been estimated to be between 64% and 90%.

Atorvastatin: After oral administration alone, atorvastatin is rapidly absorbed; maximum plasma concentrations occur within 1 to 2 hours. Extent of absorption increases in proportion to atorvastatin dose. The absolute bioavailability of atorvastatin (parent drug) is approximately 14% and the systemic availability of HMG-CoA reductase inhibitory activity is approximately 30%. The low systemic availability is attributed to presystemic clearance in gastrointestinal mucosa and/or hepatic first-pass metabolism. Plasma atorvastatin concentrations are lower (approximately 30% for Cmax and AUC) following evening drug administration compared with morning. However, LDL-C reduction is the same regardless of the time of day of drug administration.

Distribution

Amlodipine: Ex vivo studies have shown that approximately 93% of the circulating amlodipine drug is bound to plasma proteins in hypertensive patients. Steady-state plasma levels of amlodipine are reached after 7 to 8 days of consecutive daily dosing.

Atorvastatin: Mean volume of distribution of atorvastatin is approximately 381 liters. Atorvastatin is ≥98% bound to plasma proteins. A blood/plasma ratio of approximately 0.25 indicates poor drug penetration into red blood cells. Based on observations in rats, atorvastatin calcium is likely to be secreted in human milk.

Metabolism

Amlodipine: Amlodipine is extensively (about 90%) converted to inactive metabolites via hepatic metabolism.

Atorvastatin: Atorvastatin is extensively metabolized to ortho-and parahydroxylated derivatives and various beta-oxidation products. In vitro inhibition of HMG-CoA reductase by ortho-and parahydroxylated metabolites is equivalent to that of atorvastatin. Approximately 70% of circulating inhibitory activity for HMG-CoA reductase is attributed to active metabolites. In vitro studies suggest the importance of atorvastatin metabolism by cytochrome P4503A4, consistent with increased plasma concentrations of atorvastatin in humans following co-administration with erythromycin, a known inhibitor of this isozyme. In animals, the ortho-hydroxy metabolite undergoes further glucuronidation.

Excretion

Amlodipine: Elimination from the plasma is biphasic with a terminal elimination half-life of about 30-50 hours. Ten percent of the parent amlodipine compound and 60% of the metabolites of amlodipine are excreted in the urine.

Atorvastatin: Atorvastatin and its metabolites are eliminated primarily in bile following hepatic and/or extra-hepatic metabolism; however, the drug does not appear to undergo enterohepatic recirculation. Mean plasma elimination half-life of atorvastatin in humans is approximately 14 hours, but the half-life of inhibitory activity for HMG-CoA reductase is 20 to 30 hours because of the contribution of active metabolites. Less than 2% of a dose of atorvastatin is recovered in urine following oral administration.

Specific Populations

Geriatric

Amlodipine: Elderly patients have decreased clearance of amlodipine with a resulting increase in AUC of approximately 40-60%, and a lower initial dose of amlodipine may be required.

Atorvastatin: Plasma concentrations of atorvastatin are higher (approximately 40% for Cmax and 30% for AUC) in healthy elderly subjects (age ≥65 years) than in young adults. Clinical data suggest a greater degree of LDL-lowering at any dose of atorvastatin in the elderly population compared to younger adults.

Pediatric

Amlodipine: Sixty-two hypertensive patients aged 6 to 17 years received doses of amlodipine between 1.25 mg and 20 mg. Weight-adjusted clearance and volume of distribution were similar to values in adults.

Atorvastatin: Pharmacokinetic data in the pediatric population are not available.

Gender

Atorvastatin: Plasma concentrations of atorvastatin in women differ from those in men (approximately 20% higher for Cmax and 10% lower for AUC); however, there is no clinically significant difference in LDL-C reduction with atorvastatin between men and women.

Renal Impairment

Amlodipine: The pharmacokinetics of amlodipine are not significantly influenced by renal impairment. Patients with renal failure may therefore receive the usual initial amlodipine dose.

Atorvastatin: Renal disease has no influence on the plasma concentrations or LDL-C reduction of atorvastatin; thus, dose adjustment of atorvastatin in patients with renal dysfunction is not necessary.

Hemodialysis

While studies have not been conducted in patients with end-stage renal disease, hemodialysis is not expected to clear atorvastatin or amlodipine since both drugs are extensively bound to plasma proteins.

Hepatic Impairment

Amlodipine: Elderly patients and patients with hepatic insufficiency have decreased clearance of amlodipine with a resulting increase in AUC of approximately 40-60%.

Atorvastatin: In patients with chronic alcoholic liver disease, plasma concentrations of atorvastatin are markedly increased. Cmax and AUC are each 4-fold greater in patients with Childs-Pugh A disease. Cmax and

AUC of atorvastatin are approximately 16-fold and 11-fold increased, respectively, in patients with Childs-Pugh B disease.

Atorvastatin is contraindicated in patients with active liver disease.

Heart Failure

Amlodipine: In patients with moderate to severe heart failure, the increase in AUC for amlodipine was similar to that seen in the elderly and in patients with hepatic insufficiency.

5.3 Preclinical safety data

Amlodipine

Rats and mice treated with amlodipine maleate in the diet for up to two years, at concentrations calculated to provide daily dosage levels of 0.5, 1.25, and 2.5 mg amlodipine/kg/day, showed no evidence of a carcinogenic effect of the drug. For the mouse, the 2 highest dose was, on a mg/m basis, similar to the maximum recommended human dose of 10 mg amlodipine/day. 4 For the rat, the highest dose level was, on a mg/m2 basis, about twice the maximum recommended human dose.4 Mutagenicity studies conducted with amlodipine maleate revealed no drug related effects at either the gene or chromosome levels. There was no effect on the fertility of rats treated orally with amlodipine maleate (males for 64 days and females for 14 days prior to mating) at doses up to 10 mg amlodipine/kg/day (8 times the maximum recommended human dose4of 10 mg/day on a mg/m2basis). 4Based on patient weight of 50 kg

Atorvastatin

In a 2-year carcinogenicity study with atorvastatin calcium in rats at dose levels equivalent to 10, 30, and 100 mg atorvastatin/kg/day, 2 rare tumors were found in muscle in high-dose females: in one, there was a rhabdomyosarcoma and, in another, there was a fibrosarcoma. This dose represents a plasma AUC (0-24) value of approximately 16 times the mean human plasma drug exposure after an 80 mg oral dose.

A 2-year carcinogenicity study in mice given atorvastatin calcium at dose levels equivalent to 100, 200, or 400 mg atorvastatin/kg/day resulted in a significant increase in liver adenomas in high-dose males and liver carcinomas in high-dose females. These findings occurred at plasma AUC (0–24) values of approximately 6 times the mean human plasma drug exposure after an 80 mg oral dose.

In vitro, atorvastatin was not mutagenic or clastogenic in the following tests with and without metabolic activation: the Ames test with Salmonella typhimurium and Escherichia coli, the HGPRT forward mutation assay in Chinese hamster lung cells, and the chromosomal aberration assay in Chinese hamster lung cells. Atorvastatin was negative in the in vivo mouse micronucleus test.

There were no effects on fertility when rats were given atorvastatin calcium at doses equivalent to up to 175 mg atorvastatin/kg/day (15 times the human exposure). There was aplasia and aspermia in the epididymides of 2 of 10 rats treated with atorvastatin calcium at a dose equivalent to 100 mg atorvastatin/kg/day for 3 months (16 times the human AUC at the 80 mg dose); testis weights were significantly lower at 30 and 100 mg/kg/day and epididymal weight was lower at 100 mg/kg/day. Male rats given the equivalent of 100 mg atorvastatin/kg/day for 11 weeks prior to mating had decreased sperm motility, spermatid head concentration, and increased abnormal sperm. Atorvastatin caused no adverse effects on semen parameters, or reproductive organ histopathology in dogs given doses of atorvastatin calcium equivalent to 10, 40, or 120 mg atorvastatin/kg/day for two years.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Amlodipine Besylate and Atorvastatin Calcium Tablets 5mg/10mg:

Calcium Carbonate

Microcrystalline Cellulose 101

Pregelatinised Starch

Croscarmellose Sodium

Hydroxy propyl cellulose

Polysorbate 80

Microcrystalline Cellulose 102

Silica

Colloidal anhydrous

Magnesium Stearate

Opadry white 20A58875

Amlodipine Besylate and Atorvastatin Calcium Tablets 5mg/20mg:

Calcium Carbonate

Microcrystalline

Cellulose 101

Pregelatinised Starch

Croscarmellose Sodium

Hydroxy propyl cellulose

Polysorbate 80

Microcrystalline Cellulose 102

Silica

Colloidal anhydrous,

Magnesium Stearate

Opadry white 20A58875

Amlodipine Besylate and Atorvastatin Calcium Tablets 10mg/20mg:

Calcium Carbonate

Microcrystalline Cellulose 101

Pregelatinised Starch

Croscarmellose Sodium

Hydroxy propyl cellulose

Polysorbate 80

Microcrystalline Cellulose 102

Silica

Colloidal anhydrous

Magnesium Stearate

Opadry Blue 20A505029

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

Special precautions for storage

Store up to 30°C.

Protect from light and Moisture.

Keep out of reach of children.

6.4 Nature and contents of container

Blister pack of 10's (Alu-Alu) (Pack Size: 3x10 Tablets)

6.5 Special precautions for disposal and other handling

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER & MANUFACTURING SITE ADDRESS

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8. MARKETING AUTHORISATION NUMBER(S)

ATORVA AM 5/10: H2022/CTD7282/14043

ATORVA AM 5/20: H2022/CTD7283/14044

ATORVA AM 10/20: H2022/CTD7284/14045

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATON

20/11/2022

10. DATE OF REVISION OF THE TEXT

20/11/2022